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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/306,420	05/06/99	LOCARNINI S	2851-28

HM32/0407

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EXAMINER	
MOSHER,M	
ART UNIT	**PAPER NUMBER**
1648	17

DATE MAILED: 04/09/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/306,420	Locarnini et al
Examiner	**Group Art Unit**
Mary Mosher	1648

☒ Responsive to communication(s) filed on *through 1/24/2001*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-31* is/are pending in the applicat

Of the above, claim(s) *2, 3, 10, 12, 14, 15, and 19-22* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 4-9, 11, 13, 16-18, and 23-31* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892 ✓

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4* ✓

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Australia on 08 November 1996. It is noted, however, that applicant has not filed a certified copy of the AU application as required by 35 U.S.C. 119(b). Since this case was not filed under 35 USC 371, the applicant must provide the certified copy. Therefore, for purposes of examination, the effective filing date is currently 15 August 1997, the filing date of parent application PCT/AU97/00520.

Election/Restriction

Applicant's election with traverse of group I (polymerase variant virus) in Paper No. 14 is acknowledged. The traversal is on the ground(s) that the only basis for restricting the claims is an allegation that the inventions are distinct, based on their different classification, and that several groups share the same classification. This is not found persuasive because the restriction requirement also states that the different inventions involve divergent subject matter and require divergent search requirements, see page 3, next to last line. Search of group I requires search of polymerase variants; search of group II requires search of surface component variants, and search of group II requires search of variants in any two overlapping coding regions of the viral genome. These searches are not co-extensive, and therefore impose additional burden. However, on reconsideration, claims 9, 11 and 18 will be examined with group I, since these claims involve polymerase variant virus.

Applicant requests further explanation of "materially different methods" in the restriction requirement. Group I is drawn to a product, a polymerase variant virus. Group IV is drawn to methods of analysis of a polymerase mutant virus, involving analyzing a nucleotide sequence or an amino acid sequence in a particular region. Since both groups involve the polymerase in some manner, the restriction acknowledged some relationship, even though it is not one of the classical relationships of product/method of making or product/method of using. However, even though there is some relationship between the claimed virus and the claimed method of analysis, the claimed virus can be analyzed by materially different methods not requiring sequencing, such as functional analysis (escape from nucleoside treatment = resistance to nucleoside inhibitors). Therefore, the virus per se and the method of analysis of the polymerase sequence were determined to be distinct inventions, using logic similar to the logic used in determining whether or not to restrict between a product and a method of using the product. The restriction between groups II and V involved a similar analysis.

The requirement is still deemed proper and is therefore made FINAL.

Claims 2, 3, 10, 12, 14-15, and 19-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 14. Claims 12 and 21 are still withdrawn from consideration. Since the amended claims still do not specify **which protein** has substitutions at the recited positions, it still is not clear which component is involved in these claims. Therefore claims 1, 4-9, 11, 13, 16, 17, 18, and 23-31 have

been examined. Claims 4-9, 11, 17, and 18 have been examined only to the extent that they read upon the invention elected.

Applicant's request for rejoinder, based upon In re Brouwer and In re Ochia and associated training materials, is noted. If the elected product is determined to be patentable, then claims drafted to methods of making the patentable product and/or methods of using the patentable product can be rejoined with the product claims.

Claim Rejections - 35 USC § 112, second paragraph

Claims 1, 4-9, 11, 13, 16-18, and 23-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4-8, 13, 16, 18, 23-27, and 29 involve "A variant of an isolated DNA virus...resulting in at least one amino acid addition, substitution, and/or deletion....". "Variant" is a relative term. Variant compared to what? Without specifying a reference amino acid sequence, it is impossible to tell whether or not a particular sequence is "variant". This rejection is not applied to claims 9, 11, 28, and 30, because these claims contain a positive statement defining characteristics of the claimed "variant".

Claims 7, 8, 26, and 27 recite "a mutation in one or more amino acids within the sequence...". It is not clear if the claim is drawn to a virus with at least one difference from the recited sequence, or if the recited sequence specifies the required "mutation" . For example, in

claim 7, does Q or K in position 1 make the virus a claimed variant, or would the claimed variant have any amino acid *except* Q or K at position 1?

Claims 9, 11, 13, 16, 18, 28, 30, and 31 recite "reduced sensitivity" or "decreased sensitivity". "Reduced" and "decreased" are relative terms, and the claims do not provide a point of reference for determining what is "reduced". Also, the recitation "such as" renders the claims indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention.

Regarding claim 17, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). It is also unclear what is intended by the recitation "Accordingly, the present invention is directed to" at the beginning of the claim.

For these reasons, the claims are seen as indefinite.

In addition, the claims are directed to "a variant of an isolated DNA virus...". It is not clear if this claim language describes the actual subject matter the inventors wish to claim. The specification teaches the characterization of several patient samples containing human hepatitis B virus, obtained from patients treated with nucleoside analogs. The virus in these samples contain mutations which alter the amino acid sequence of the polymerase and/or the S antigen in specific regions, and knowledge of mutations in these regions is certainly useful for purposes of diagnosis and/or choice of treatment regimes. However, the claims under examination are directed to "a variant of an isolated virus", and this language raises a number of troubling issues, which are

discussed briefly here and in more detail below. (1) It is not clear if the claims, as written, read upon unpatentable products of nature, since the claims are directed to a variant, which is itself not necessarily isolated. (2) It is not clear that the specification teaches how to *make* a variant virus, except to obtain it from a patient. (3) If the only method of making a variant virus is to obtain it from a patient, one cannot predict what variant viruses will actually arise in patients. Therefore it is not apparent that there is an adequate written description sufficient to support the full scope of the variant viruses claimed. (4) It is not clear how one would *use* all of the claimed variant viruses. The only use disclosed for the variant viruses is for development of assays, but the specification does not teach how to use viruses *per se* in developing assays, or teach the point of assays which involve viruses that do not arise in patients. For these reasons, would claims directed to methods of analysis actually better describe the subject matter of the invention? In spite of the restriction made in this application, the examiner is willing to consider examining some claims directed to methods of analysis, particularly if the claims focus upon detection of applicant's specific disclosed mutations in human hepatitis B virus (and are not broadly directed to detecting any mutation in polymerase domain B or C or any mutation altering the overlapping region AA118-207 of the S antigen, for any para-retrovirus or any nonhuman hepatitis B virus).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 4-9, 11, 13, 16, 17, 18, and 23-31 are rejected under 35 U.S.C. 101 because, as written, the claims read upon nonstatutory products of nature. The claimed "variants" are identical to viruses which arise in nature (although selection of the variants is certainly enhanced by nucleoside treatment of patients). Because the claims do not actually state that the variant virus is isolated, the claims are rejected.

Claim Rejections - 35 USC § 112, first paragraph, description

Claims 9, 11, 13, 16-18, and 28-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the full scope of the claimed invention. This is a "written description" rejection.

(A) Claims 9, 11, 13, 16, 18, 28, and 30 all are drawn to nucleoside-resistant virus. (B) Claims 16 and 29 are both drawn to viruses which simultaneously mutated polymerase sequence and reduced immunoreactivity of the S antigen. (C) Claim 17 is drawn to any HBV which has at least 60% similarity to SEQ ID NO:17. The groups A-C are each drawn to a genus of materials. All three genera encompass materials with substantial variation and unpredictable characteristics. In (A), the claims specify a region which is mutated, and a (rather long) list of potentially variant amino acids. However, the specification discloses only a limited subset of mutations which actually confer the required nucleoside resistance, and there is no guidance as to which of the additional recited variants actually possess the required nucleoside resistance. Since the effect of

changing even a single amino acid in an enzyme is unpredictable in regard to whether or not it affects the nucleoside sensitivity of the enzyme, it is concluded that the specification does not reasonably convey possession of the full scope of the genus as claimed. Similarly, in group (B), the specification again teaches a limited number of species which contain reduced immunoreactivity, and these teachings do not permit one skilled in the art to predict which of the many possible other alterations also reduce immunoreactivity. In group (C), the only common characteristic of the genus is that is comprises a genome segment 60% similar to SEQ ID NO:17. This reads upon many species of virus, with widely varying and unpredictable characteristics, including viruses which have yet to be discovered. Because of the widely varying and unpredictable characteristics of viruses embraced within the broadly claimed genera A-C, in contrast to the limited number of species disclosed as working examples in the specification, it is concluded that the disclosure in the specification does not reasonably convey possession of the full scope of the broadly claimed variants.

Claim Rejections - 35 USC § 112, first paragraph, enablement

Claims 1, 4-9, 11, 13, 16, 17, 18, and 23-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection has several aspects, each discussed in a separate paragraph below.

First, the claims are drawn to variant viruses. The specification teaches isolation of DNA of human hepatitis B virus from patient samples, but does not teach how to obtain the viruses themselves. Furthermore, the claims are drawn to a genus of variant viruses. The specification does not teach methods to create variant viruses in vitro, or teach in vivo sources for the full scope of variant viruses. Furthermore, the specification does not provide any guidance at all regarding DNA viruses which replicate via an RNA intermediate, other than human hepatitis B virus. Because of the limited teachings regarding how to make viruses, the absence of teachings for viruses other than hepatitis B, the lack of working examples of viruses per se, and the broad scope of the claims, it is concluded that undue experimentation would be required to make the variant viruses claimed.

Second, regarding how to use the claimed viruses, the specification discusses (on pages 2 and 10) developing assays to monitor therapeutic regimes and screen for agents which can mask effects of mutation. Although those skilled in the art would be readily able to use nucleotide and amino acid sequence information to design assays and screening methods, it is not apparent how one would use the virus itself. Furthermore, claims 1, 4-8, 17, and 23-27 encompass mutations which do not have any disclosed functional effect, and it is not clear how one would use an assay which detects a "silent" sequence variant. Still further, if the use of the viruses is for diagnosis of escape mutations (in either or both of the polymerase and the surface antigen), only some species within the genus have actually been found to occur in patients, and the specification does not teach how to use an assay which detects mutant viruses that do not exist in patients. For these

reasons, it is concluded that undue experimentation would be required to use the variant viruses, as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by Chenault et al (Biochimie 76:3-8, 1994). See Tables III and IV regarding non-silent variations and deletions in ORF 5, encoding the polymerase (reverse transcriptase).

Claims 1, 4-8, 11, and 23-27 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Fischer et al (Antimicrobial Agents and Chemotherapy 40(8): 1957-1960, August 7, 1996). See Figure 1 and page 1959, regarding the virus M1512VM.

Claims 1, 4-8, 17, 23-26 and 29 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Norder et al (Virology 198:489-503, 1994). See Figure 1, about nucleotide 580, for a variant which results in at least one amino acid substitution in the both polymerase B region and surface protein. See also around nucleotides 160, 620, and 750 for other variants meeting claim limitations.

Claims 1, 4-6, 9, 11, 17, 23-25, and 28-31 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Tipples et al (Hepatology 24(3): 714-717, September 1996). See Figure 2.

Claims 1, 4- 9, 11, 13, 16-18, and 23-31 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Ling et al (Hepatology 24(3): 711-713, September 1996). See Figure 2.

Claims 1, 4-9, 13, and 17 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Bartholomew et al (Lancet 349:20-22, January 1997). See Figure 1.

WO 97/40193, issued 30 October 1997 (not available as prior art) is cited as of interest, in disclosing nucleoside-resistant polymerase variant HBV genomes, see Figure 1 and page 10. Note that the patent's polymerase codon numbering differs slightly from applicant's: the M in YMDD is 550 for applicants, 552 for the patent.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary E. Mosher, Ph.D. whose telephone number is (703) 308-2926. The examiner can normally be reached on Monday -Thursday and alternate Fridays from 6:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for this Group is now (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

April 6, 2001

MARY E. MOSHER
PRIMARY EXAMINER
GROUP 1800
1600